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## review

## Intellectual functioning in schizophrenia: a marker of neurodevelopmental damage?

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There is abundant evidence that neurocognitive deficits are present in schizophrenic patients (Aylward *et al.* 1984). A recent meta-analytical review of 22 neurocognitive test variables concluded that schizophrenia is characterized by a broadly based, moderately severe ( $d = 0.6$ ) cognitive impairment, with varying degrees of deficit in all domains (Heinrichs & Zakzanis 1998). In comparison with learning disability these deficits are mild, with around 50% of patients scoring in the deficit range on most tests of cognitive function (Green 1998). This review will summarize some of the key findings regarding the relationship of cognitive deficits to the aetiology of schizophrenia.

### Neurodevelopment or neurodegeneration?

Until the mid-1980s, cognitive deficits in schizophrenia were thought to result from a neurodegenerative process that was assumed to underlie the disorder. However, neuropathological, epidemiological and neuroimaging evidence began to suggest that schizo-

phrenia may instead be associated with a relatively static neuropathology, arising early in life, that predisposed the individual to express the disorder in adulthood. Schizophrenia was thus reformulated as a neurodevelopmental disorder (Murray & Lewis 1987; Weinberger 1987), and this model has now gained wide acceptance. In its current form, the neurodevelopmental hypothesis of schizophrenia proposes that genetic and early environmental factors interact to disrupt cortical development *in utero*, resulting in the formation of abnormal connections during childhood. These abnormalities become manifest in adolescence when they disrupt brain maturation, possibly through abnormalities of myelination or an excess of normal synaptic pruning (Takei & Murray 1998). This neurodevelopmental insult is thought to interact with later environmental factors leading to the onset of schizophrenia (Murray & Fearon 1999). Although the precise nature of the neurodevelopmental insult in schizophrenia is not understood, it certainly seems plausible that such damage would adversely affect performance on cognitive tests.

The hypothesis that neurocognitive deficits in schizophrenia are the result of neurodevelopmental damage leads to three key predictions: that cognitive deficits will be a fundamental part of the illness (as opposed to a side-effect of treatment), will be present

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before the onset of clinical symptoms, and will not necessarily deteriorate over time.

### **Antipsychotic drugs**

Are cognitive deficits intrinsic to schizophrenia, or are they merely an unfortunate side-effect of its treatment? Conventional neuroleptic drugs probably confer a modest overall beneficial effect on neurocognition (Green 1998), although assessment of these effects may be confounded by sedation and motor side-effects. A further difficulty is that anticholinergic drugs, which are known to have a detrimental effect on memory in schizophrenia (Baker *et al.* 1983; Sweeney *et al.* 1991), are frequently co-administered with conventional neuroleptics in an attempt to reduce extrapyramidal side-effects. With modern 'atypical' antipsychotics the situation is clearer, with two recent reviews concluding that these drugs do not diminish, and probably slightly enhance, cognitive function (Weiss *et al.* 2002; Kasper & Resinger 2003).

### **Premorbid cognitive deficits**

To establish whether cognitive deficits are present before the onset of illness requires the use of prospectively collected, population-based data. In the past few years, several such studies have examined premorbid cognitive function, using prospectively ascertained school records and neuropsychological batteries (Done *et al.* 1994; Jones 1995; David *et al.* 1997; Isohanni *et al.* 1998; Cannon *et al.* 1999, 2002a; Cannon *et al.* 2000; Davidson *et al.* 1999; Fuller *et al.* 2002; Gunnell *et al.* 2002; Walker *et al.* 2002; reviewed in Cannon *et al.* 2003). Taken together, these studies provide strong evidence of cognitive and other developmental abnormalities in children who would later develop schizophrenia, in a dose-response relationship – the worse the cognitive function, the higher the risk of schizophrenia (Cannon *et al.* 2003). There is also evidence that decline in cognitive functioning during childhood is associated with later schizophrenia. Thus Kremen and others (Kremen *et al.* 1998) showed that decline in IQ score between ages 4 and 7 years was a better predictor of schizophreniform disorder at age 23 than either IQ at age 7 or socio-economic status. Fuller and others examined scores on standardized cognitive tests at

ages 9, 13 and 16 in patients who later developed schizophrenia. Compared with population norms, the preschizophrenic children had significantly lower scores only at age 16, and a significant drop in scores between ages 13 and 16 (Fuller *et al.* 2002). This premorbid deterioration in cognitive function was interpreted by the authors as suggestive of excessive synaptic pruning in the preschizophrenic patients.

### **Genetic or environmental?**

The neurodevelopmental hypothesis of schizophrenia suggests that both genetic and environmental factors can lead to abnormal neurodevelopment. Are premorbid cognitive deficits markers of genetic or environmental aetiological factors? High risk studies have shown that the children of schizophrenic parents display abnormalities in cognitive function (Ott *et al.* 1998; Byrne *et al.* 1999), suggesting that genetic factors may be responsible. But such associations could be confounded by the social effects of having a psychotic parent. A more rigorous approach would be to compare the cognitive function in childhood of unaffected siblings of schizophrenic subjects with that of the normal population. Using this method, Cannon and colleagues (Cannon *et al.* 2000) showed that unaffected siblings of schizophrenic subjects performed worse than controls at two time points, but nevertheless tended to outperform their affected siblings.

### **Early environmental insults**

A recent meta-analysis, using only prospective population studies, confirmed the association of low birth-weight, asphyxia and other pregnancy and birth complications (PBCs) on the risk for schizophrenia (Cannon *et al.* 2002b). A number of PBCs have been found to have a negative impact on adult intelligence in normal samples, including antenatal hypoxia (Naeye & Peters 1987; Seidman *et al.* 2000), low birth weight (Seidman *et al.* 2000; Matte *et al.* 2001) and neonatal malnutrition (Lucas *et al.* 1998). Could cognitive abnormalities in schizophrenia therefore be mediated by PBCs? Goldstein and colleagues (Goldstein *et al.* 2000) failed to find an effect of probable hypoxic damage on IQ at age 7 in individuals who were genetically predisposed to schizophrenia. Fur-

thermore, three prospective cohort studies have demonstrated little change in the relationship between cognitive function and schizophrenia when adjusting for PBCs (Cannon *et al.* 2000; Cannon *et al.* 2002a; Gunnell *et al.* 2002), although one found an association between PBCs and unusual movements at 4 years (Rosso *et al.* 2000). Thus it appears that that cognitive deficits are more strongly associated with genetic than early environmental risk factors, but further work is needed in this area.

### Social factors

Cognitive function is known to correlate with a number of sociodemographic factors (Crandell & Hobson 1999), and both the risk of schizophrenia and the likelihood of psychiatric referral may be similarly influenced (Verhaak 1995). Social factors could mediate the association between cognitive dysfunction and schizophrenia in two ways. The first possibility is confounding, whereby certain social factors predispose both to poor cognitive performance and to schizophrenia. Possible confounders include low socio-economic group, urban birth and being a migrant. The second possibility is that social deprivation leads to abnormal neurodevelopment, which in turn causes both cognitive impairment and schizophrenia. Unfortunately there has been little work in this area.

### Longitudinal stability of cognitive deficits after illness onset

Rund reviewed 15 longitudinal studies with a follow-up of at least 1 year and found no evidence of cognitive decline (Rund 1998). Gold and colleagues administered a cognitive test battery to 54 patients at illness onset and again at 5 years. Patients significantly improved in most areas of cognitive function including performance IQ, and did not deteriorate on any measure other than motor speed (Gold *et al.* 1999). Some of the improvement was accounted for by improvement in positive symptoms, but not by changes in antipsychotic or anticholinergic medication. Heaton studied 142 schizophrenic patients and 206 normal controls over an average of 3 years. Both the schizophrenic and control subjects improved, with no difference in improvement between cases and

controls. However, the situation in elderly patients with schizophrenia may be different. Freidman, Harvey and colleagues (Friedman *et al.* 2001) followed up 107 schizophrenia patients, ranging in age between 20 and 80 years, for 6 years. Cognitive performance was relatively stable before age 50, but there was marked decline in older subjects, which was greater than that observed in healthy controls.

### Conclusion

Cognitive deficits in schizophrenia are widespread, and are not secondary to drug treatment. They are present prior to disease onset, may be partly genetic and are probably not simply a result of PBCs. There may be some widening of the gap between preschizophrenics and controls during childhood, but the deficits appear to relatively remain stable for the initial years after illness onset. There may be further decline in older patients with schizophrenia. These findings are compatible with the model that cognitive deficits represent a marker of neurodevelopmental damage in schizophrenia, and may track a neurodegenerative process later in the course of the illness.

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